American Journal of Hematology 54:202–208 (1997)

Autologous Bone Marrow Versus Non-Mobilized Peripheral Blood Stem Cell Transplantation for Lymphoid Malignancies: A Prospective, Comparative Trial

Daniel J. Weisdorf,[1,4,*] Catherine M. Verfaillie,[1,4] Wesley J. Miller,[1,4] Bruce R. Blazar,[2,4] Elizabeth Perry,[3,4] Xiao Ou Shu,[2,4] Kathleen Daniels,[4] Peter Hannan,[4] Norma K.C. Ramsay,[2,4] John H. Kersey,[2,3,4] and Philip B. McGlave[1,4]

[1]Department of Medicine, University of Minnesota, Minneapolis
Department of Pediatrics, University of Minnesota, Minneapolis
[2]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis
[3]Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis
[4]Bone Marrow Transplantation Program, University of Minnesota, Minneapolis

Autologous transplantation using bone marrow stem cells (BMSC) or peripheral blood stem cells (PBSC) is widely used for non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). We report a randomized, comparative trial comparing BMSC vs. non-mobilized PBSC for responsive NHL or HD. Patients randomized to BMSC (n = 13) vs. PBSC (n = 15) had more rapid neutrophil recovery (median 23 vs. 30 days), RBC independence (25 vs. 62 days), platelet independence (24 vs. 54 days), and shorter hospital stay. However, neither relapse, overall survival, nor relapse-free survival were different receiving BMSC vs. PBSC (all *P* > .7). Concurrently, 54 others (34 BMSC, 20 PBSC) were assigned non-randomly because of resistant disease or marrow unsuitable for harvest and similar patterns of engraftment favoring BMSC over PBSC were observed. In the entire group, BMSC transplantation (n = 47) led to quicker neutrophil recovery (*P* = .02), RBC (*P* = .06), and platelet independence (*P* = .04) and earlier hospital discharge (*P* = .02) vs. PBSC (n = 35). No difference in relapse, overall, or relapse-free survival were observed using BMSC vs. PBSC. These data suggest that non-mobilized PBSC are a satisfactory alternative to BMSC in patients with unsuitable marrow; however, transplantation with non-mobilized PBSC was associated with slower hematologic recovery, and longer hospital stay. No difference in tumor recurrence rates was observed between the PBSC or BMSC recipients. Unprimed PBSC transplantation offered no clinical advantage to BMSC.
Am. J. Hematol. 54:202–208, 1997

Key words: autologous; bone marrow transplantation; blood stem cells; lymphoma

INTRODUCTION

The widespread application of autologous transplantation for both non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) has identified two limitations of this therapy. First, treatment-associated morbidity, primarily due to infectious and hemorrhagic complications during the early post-transplant pancytopenia, can prolong hospitalization and raise costs. Much more significant and more frequent is the problem of malignant relapse which can arise either from endogenous residual tumor that escapes eradication by the pre-transplant conditioning therapy or from inadvertently collected and

Contract grant sponsor: National Cancer Institute; Contract grant number: CA21737.

*Correspondence to: Daniel Weisdorf, Box 480 UMHC; 420 Delaware Street SE, Minneapolis, MN 55455.

Received 25 April 1996; Accepted 9 October 1996.

cryopreserved, clonogenic tumor cells [1–10]. Both marrow cells collected by aspiration harvest and circulating peripheral blood stem cells (PBSC) collected by leukopheresis have been used for successful transplantation. It has been suggested by some investigators that PBSC might be favored over bone marrow stem cells (BMSC) because of enrichment for committed progenitors, quicker neutrophil recovery [11,12], and because the PBSC might contain fewer malignant cells [7,13]. However, within PBSC collections, the content of true, multipotent, hematopoietic stem cells with self-renewal capacity is uncertain and the potential for incomplete engraftment or continuing poor marrow function has been questioned.

To address the comparative value of these two stem cell sources, we performed a randomized trial comparing PBSC to BMSC. This trial was initiated in 1989, before the widespread use of recombinant cytokines for progenitor cell mobilization. Therefore, both stem cell sources were collected without either chemotherapy or growth factor mobilization. Additionally, concern was raised that mobilization with either chemotherapy or growth factors might alter either (1) tumor growth and/or distribution or (2) committed and primitive hematopoietic progenitor cell growth and repopulating capacity. Concurrently, patients ineligible for randomization because of resistant disease or unsuitable marrow were transplanted using an assigned stem cell source. Because of limited patient numbers, their outcomes are analyzed in conjunction with the randomized patients' data. We report here the results of this prospective comparative trial including both the randomized and assigned patients' multi-lineage engraftment as well as the consequences of possible tumor contamination by evaluation of malignant relapse-free survival.

PATIENTS AND METHODS

The study design included enrollment of patients with chemotherapy-sensitive non-Hodgkin's lymphoma or Hodgkin's disease who were candidates for autologous transplantation. All patients were required to have a remission bone marrow (by light microscopic evaluation) with adequate cellularity ($\geqslant$25%) to be collectible by aspiration harvest. Consenting patients were randomly assigned to either BMSC with a harvest cell dose target of 2×10^8 nucleated cells/kg or to PBSC collected by leukopheresis in six collections, usually Monday, Wednesday, and Friday of two succeeding weeks totaling a minimum of three and a target collection of 6×10^8 cells/kg. The leukophereses for PBSC collections were performed over 3–4 h each, processing 10–12 liters of blood on a Fenwal CS3000 cell separator using a modification of Program One. Neither recovery from chemotherapy nor hematopoietic growth factor therapy was used to mobilize PBSC in this trial. Insufficient data on clonogenic progenitor content or CD34 content of the cryopreserved stem cells were available for statistical analysis. Prior to randomization, patients were stratified by diagnosis and into cohorts who had no previous bone marrow tumor involvement, those who had previous bone marrow tumor but none present within 3 months prior to harvest, or to a third group who had a remission bone marrow at the time of harvest but had previous bone marrow tumor recognized morphologically within the preceding 3 months.

While 28 patients were enrolled in this randomized trial, during this period of time, 55 additional patients received autotransplantation for the NHL or HD and were assigned to either BMSC ($n = 34$) or PBSC ($n = 20$). One patient received both PBSC and BMSC and was excluded from further analysis. Two patients randomized to PBSC received supplemental BMSC because of insufficient PBSC collections; they are analyzed as randomized. The other 54 patients transplanted, but assigned (not randomized) to either BMSC or PBSC were prospectively excluded from the randomization for the following reasons: 7 patients had unstable, but responsive lymphoma considered unsuitable to wait for PBSC collections; 5 had non-responsive lymphoma and were ineligible for randomization; thus all received BMSC. Fifteen patients had either persistent morphologic bone marrow tumor or hypocellular marrow; they received PBSC. Fourteen patients refused consent for randomization, though they consented to transplantation. Neither the attending physicians nor the patients were allowed to choose PBSC and thus these patients were all assigned a marrow stem cell source. Thirteen others (8 BMSC; 5 PBSC) were assigned because of combinations of the above reasons (usually unstable though responsive malignancy and/or marrow unsuitable for harvest).

Patients with NHL were conditioned using cyclophosphamide (60 mg/kg × 2) and fractionated total body irradiation (165 cGy × 8 totaling 1,320 cGy) as previously described [6]. Hodgkin's disease patients and NHL patients ineligible to receive TBI received cyclophosphamide (1,500 mg/m^2/d × 2), carmustine (300 mg/m^2), and etoposide (150 mg/m^2 BID × 3 days) as described [9]. All patients were nursed in single rooms on the University of Minnesota Bone Marrow Transplantation Unit with high-efficiency particulate air (HEPA) filtration and simple handwashing as protective isolation. Other supportive care practices for this population were previously reported from our institution [6,14]. Forty of these patients were enrolled in a prospective, Phase I dose escalation trial of recombinant human IL-1α (Immunex Corporation, Seattle, WA) which included patients with non-responsive disease, as described [14]. Twenty-seven patients received $\leqslant$1.0 μg/m^2/day IL-1α, a dose which had no apparent effect on acceleration of engraftment

TABLE I. Patient Characteristics

	Randomized (n = 28)[a]			Assigned (n = 54)	
	BMSC	Probability*	PBSC	BMSC	PBSC
N	13		15	34	20
Age (years)	39 (9.9–53)	$P = 0.81$	37 (9.9–65)	39 (8.7–62)	36 (26–63)
Male:female	6:7	$P = 0.27$	10:5	23:11	15:5
Hodgkin's disease	2	$P = 0.22$	6	7	8
Non-Hodgkin's lymphoma	11		9	27	12
CR/PR at transplant	11		12	29	16
Interval, diagnosis to transplant [Median (range), months	17 (3.7–90)		15 (6.3–74)	16 (4.7–108)	27 (5.3–114)
IL-1α (3.0 μg/m^2/d)	2		1	8	2

[a]Two randomized patients receiving BMSC in addition to PBSC because of insufficient PBSC collections.
**P* values represent a Chi square comparison (*t*-test for age) of clinical characteristics between patients randomized to BMSC vs. PBSC.

[14]. Their outcomes are evaluated along with 42 who received no IL-1α and contrasted with 13 patients who received higher dose (3.0 μg/m^2/day) IL-1α. The impact of IL-1α therapy on the results of this trial was analyzed using Cox model multivariate regression. No other patients received pre-harvest or post-transplant growth factors, except those with a leukocyte count below 300/μl on day +21 or a neutrophil count < 300/μl on day +28 who received GM-CSF as salvage therapy for delayed engraftment [15].

STATISTICAL ANALYSIS

Statistical analysis was performed using Chi-square comparisons or Student's *t*-test (for age) of pre-transplant characteristics and Kaplan-Meier calculations for estimates of the rate of engraftment, relapse, and survival as appropriate [16]. The randomized cohorts were compared by intent-to-treat analysis. Univariate comparisons between groups were performed using the Mantel-Cox test statistic. Multivariate analyses were performed using Cox model regression analyses [17]. In addition, to evaluate observations in the randomized cohort and the entire group including the assigned patients, these regression models were tested for the effect of stratification by randomization group (pooled over strata) on the intent to treat comparisons of BMSC vs. PBSC. The median follow-up from transplantation for surviving patients surviving relapse-free is 1.3 years with the longest relapse-free survivors alive beyond 3.5 years from transplantation.

RESULTS

The clinical and demographic characteristics of the patients are shown in Table I. Twenty-eight patients were enrolled in the randomized trial. The median age was 37; only four patients were children. Eight patients had Hodgkin's disease and 20 had NHL. Among the patients assigned to stem cell source, a similar distribution of age, sex, and underlying disease was observed. Twenty-three of the 28 randomized patients were in complete remission (CR) or partial remission (PR) at the time of transplantation. Within the total of 82 patients treated, nine were in CR, one had primary refractory disease, 59 were in PR, and 14 had resistant relapse. The patients randomized to BMSC (n = 13) received a median of 2.24×10^8 cells/kg (range 1.79–3.78) similar to the median of 2.20×10^8/kg for the whole BMSC population, while those randomized to receive PBSC (n = 15) received a median of 5.34×10^8 cells/kg (3.81–7.21), which also was similar to the median of 5.95×10^8 cells/kg received by the whole PBSC population. Three of the randomized (2 BMSC; 1 PBSC) patients and 10 of the assigned patients received the higher dose of IL-1α (3.0 μg/m^2/day) for the first 14 days after transplant.

Engraftment

The results for the primary study endpoint, that of differential rates of engraftment between BMSC and PBSC patients, are displayed in Table II. As shown, those randomized to BMSC achieved 0.5×10^9 neutrophils/L at a median 1 week sooner than those randomized to receive PBSC. Though limited patient numbers in the randomized trial compromised the statistical power of the analysis, a similar 1-week delay was observed in median time to neutrophil recovery of those assigned, but not randomized to receive PBSC. In the whole group, the observed differences between BMSC and PBSC recovery were statistically significant ($P = .02$). Similarly, the time to RBC and platelet transfusion independence was shorter in patients receiving BMSC than in those receiving PBSC. This was true for both the randomized group and those assigned a stem cell source since a 4-week

TABLE II. Time to Engraftment†

	Randomized*		Assigned		
	BMSC	PBSC	BMSC	PBSC	Probability**
N	13	15	34	20	
Neutrophils ⩾ 0.5×10^9/L (days)	23 (11–53)	30 (11–104)	18 (9–38)	25 (11–117)	$P = .02$
RBC independence	25 (7–182)	62 (15–104)	31 (9–124)	43 (11–182)	$P = .06$
Platelet independence	24 (13–182)	54 (18–104)	30 (9–11)	42 (15–182)	$P = .04$

†Shown are the median (range) of days to engraftment. The time (days) to absolute neutrophil count (⩾0.5×10^9/L), RBC independence (no RBC transfusions in the subsequent 30 days) and platelet independence (no platelet transfusions for ⩾15 days) are shown. One randomized and 4 assigned BMSC patients died before trilineage engraftment and were censored; 3 randomized and 3 assigned PBSC patients were censored similarly.
*In the randomized group, log rank comparisons were: neutrophils, $P = .13$; RBC, $P = .62$; platelets, $P = .34$.
***P* values reflect univariate, log-rank, Kaplan-Meier comparisons of differences between PBSC vs. BMSC in all patients, randomized and assigned.

delay in RBC and platelet recovery was seen for PBSC recipients in the randomized group and a similar, though smaller, difference was observed in the assigned population. Though not statistically significant within the randomized cohort, in the whole group this delay in platelet transfusion independence was statistically significant ($P = .02$) and there was a strong trend observed for red cell independence ($P = .06$), both findings favoring BMSC over PBSC.

This modestly accelerated trilineage engraftment with BMSC was accompanied by quicker time to hospital discharge alive. In the randomized cohort of patients, the median hospital discharge time was 33 days after receiving BMSC (range 19–52) and 10 days later in those randomized to PBSC (median 43 days; range 21–69 days; $P = 0.13$). Similarly, a 7-day-earlier discharge was observed in those assigned BMSC vs. PBSC (BMSC median 30 days; range 13–59 vs. PBSC median 37 days; range 21–85) ($P = .03$).

Because this analysis included patients with HD as well as NHL as well as a cohort (primarily the nonrandomized patients) participating in a Phase I trial of IL-1α to accelerate engraftment, we performed a series of Cox model multivariate analyses to assess the independent contribution of stem cell source in relation to other factors potentially associated with the accelerated trilineage engraftment and quicker discharge observed with BMSC. These multivariate analyses potentially considered patient age (in decades), diagnosis (HD vs. NHL), disease status (CR or PR pretransplant vs. refractory disease), IL-1α dose (0–1.0 μg/m^2/day vs. ⩾3.0 μg/m^2/day), stem cell source (BMSC vs. PBSC), and were stratified over the randomized and assigned patient groups. Among these variables considered in the multivariate analysis, there was a significant association between important covariates, e.g., Hodgkin's Disease patients more frequently received PBSC ($P = .03$). However, as shown in Table III, these regression models demonstrated a significant advantage favoring the use of BMSC over PBSC for both neutrophil, red cell, and platelet engraftment across the randomized and the assigned groups. High-dose IL-1α had an additional, independent effect on accelerated neutrophil recovery. Transplantation for responsive disease pre-transplant and for Hodgkin's disease was also associated with an independently significant, favorable effect on RBC and platelet recovery.

TABLE III. Factors Favoring Accelerater Engraftment: Multivariate Analysis*

	Relative risk ratio	Probability
Time to neutrophils > 0.5×10^9/L		
BMSC	2.1	.004
IL-1α 3.0 μg/m^2/d	2.7	.001
Time to RBC independence		
BMSC	2.8	.0003
Hodgkin's disease	1.9	.01
CR/PR pre-transplant	5.9	.0001
Time to platelet independence		
BMSC	3.6	.0001
Hodgkin's disease	3.4	.0001
CR/PR pre-transplant	9.1	.0001

*Shown are the independently significant favorable factors, and the relative risk for the 3 lineage specific engraftment endpoints. In the patients randomized to a stem cell source, Hodgkin's disease patients had a RR of 9.1 (favoring quicker platelet engraftment [$P = 0.02$]) while in the assigned patients, Hodgkin's disease patients had an RR of only 2.5 ($P = 0.006$). No other variables had a significant interaction with randomized or assigned stem cell source. *P* values represent the results of Cox regression models testing the independent significance of each variable's association with the engraftment endpoint.

Six of the 82 patients died without sustained neutrophil recovery. Two had persisting, aggressive lymphoma and two died early (day +15, +18) with sepsis and multiorgan failure. Two patients, both receiving PBSC (1 randomized, 1 assigned) died of graft failure on day +55 and +104 after transplantation. All other patients had sustained trilineage engraftment.

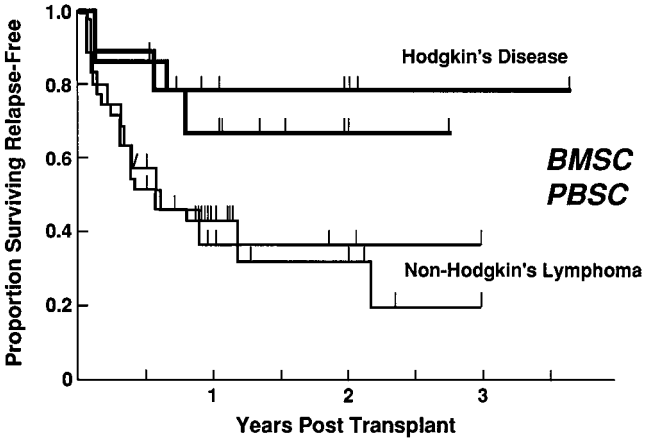

Fig. 1. Relapse free survival after bone marrow or peripheral blood stem cell transplantation for Hodgkin's disease or non-Hodgkin's lymphoma. No differences in the proportion surviving disease-free using either stem cell source within each diagnosis subgroup are noted ($P > 0.5$). Tick marks represent patients surviving without malignant relapse after transplantation.

Malignant Relapse and Survival

Because the original hypothesis of differential tumor contamination in BMSC vs. PBSC might lead to differential relapse after transplantation, we also examined the clinical outcomes related to disease relapse. At 2 years post-transplant, patients randomized to receive BMSC had a 63% (26–100%; 95% confidence interval) relapse risk compared to 38% (11–65%) for patients randomized to PBSC ($P = 0.9$) while those assigned to BMSC had a 58% (34–82%) relapse risk compared to 49% (21–77%) for those assigned to PBSC ($P = 0.46$). In addition, 2-year relapse-free survival was similar in those randomized and those assigned a stem cell source (randomized BMSC 34% [0–68%]) vs. PBSC 53% (27–79%) ($P = .89$) and assigned BMSC 37% (15–59%) vs. PBSC 36% (12–60%). Comparisons between the stratification groups with either no, recent, or remote marrow tumor involvement revealed no important or even suggestive differences in outcome (not shown). However, because patients with NHL had a substantially higher relapse risk, we examined the relapse potential of the two stem cell source groups within the separate diagnostic categories. For the randomized and the assigned group, patients with NHL receiving BMSC had a 70% (36–100%) risk of relapse after transplantation compared with PBSC 53% (16–90%) ($P = 0.6$). In contrast, fewer relapses were seen in patients with Hodgkin's disease using either stem cell source. We observed zero relapses in those HD patients receiving BMSC vs. 20% (0–56%) relapse with PBSC ($P = 0.53$). The impact of stem cell source on ultimate relapse-free survival is shown in Figure 1. We observed nearly equivalent outcomes within each stem cell source group, whether randomized or assigned. As shown, though Hodgkin's patients had a superior outcome, no differences in relapse-free survival between BMSC or PBSC groups were observed. Likewise, in the NHL cohorts, BMSC and PBSC patients had similar relapse free survival ($P > 0.5$).

To confirm the validity of these findings, we performed a series of Cox model multivariate analyses to examine factors associated with survival, relapse risk, and relapse-free survival and considered the potential importance of stem cell source, diagnosis, age, disease status, and IL-1α therapy, as well as a statistical effect of being randomized or assigned to a stem cell source. In these regression models, the independently significant important factors included only chemotherapy responsiveness and disease burden before transplantation (CR/PR pre-BMT). No independent effect of the stem cell source, whether randomized or assigned on any of these three clinical endpoints, was observed (all $P > 0.5$; data not shown).

DISCUSSION

PBSC transplantation has become increasingly popular due to its application for a wide variety of tumors, its postulated association with quicker engraftment, and its potential for lesser tumor contamination and lower risk of relapse. Though our analysis had only limited statistical power in the randomized group, none of these associations could be corroborated in this study testing non-mobilized PBSC. As originally reported by investigators from Nebraska and Australia [5,11], PBSC transplantation can successfully rescue patients receiving myeloablative therapy and restore multilineage engraftment in a reasonably short period of time [18]. More recently, the use of mobilized PBSC collected during recovery from myelosuppressive chemotherapy [19,20, see 26] or induced by hematopoietic growth factors [21–27] has resulted in substantially quicker engraftment and possibly shorter hospital stay, reduced in-hospital morbidity, and lower cost. It must be cautioned that not all the recently reported mobilized PBSC transplant trials have included fully myeloablative preconditioning, thus potentially allowing endogenous hematopoietic stem cells to proliferate and then restore hematologic and immunologic competence. Nonetheless, it is well established that both resting and mobilized PBSC collections contain both committed and primitive hematopoietic progenitors with multilineage potential and stem cell-like functional capacity able to restore lymphohematopoietic competence. In the current trial, however, using unmobilized PBSC compared to unmobilized BMSC, we observed neither acceleration of multilineage engraftment nor reduction in in-hospital morbidity, mortality, or costs in association with PBSC transplantation. In both the randomized and assigned cohorts, BMSC was favored for

these outcome measures compared to non-mobilized PBSC.

While these findings do not dispute the recent favorable observations of shortened pancytopenia with chemotherapy or growth factor-mobilized PBSC, in the absence of exogenous mobilizing agents, BMSC remain the preferred choice. In this trial, BMSC transplantation was associated with quicker engraftment of neutrophils, red cells, and platelets. However, if BMSC were unavailable as a source for harvest because of either bone marrow tumor or marrow hypocellularity, then non-mobilized PBSC were a satisfactory and viable stem cell source for autologous transplantation.

Clarification of the importance of harvested stem cells as a source of clonogenic tumor potentially able to induce malignant relapse requires additional study. While some studies have described recognition in harvested cells of tumor-associated DNA sequences after in vitro culture, by Southern blot [13] or by polymerase chain reaction [28,29], there is no definitive evidence that cells containing this tumor-associated DNA are the source of relapse post-transplant. Investigators from the Dana Farber Cancer Institute have reported that purgability of BMSC to a PCR-negative state was associated with favorable outcome after marrow transplantation [29]; however, these investigators have also found a high incidence of tumor-associated DNA in the peripheral blood of NHL patients [30]. At least in leukemia patients [31], early retroviral gene marking studies have showed that clonogenic tumor cells within the harvested marrow may contribute to post-transplant relapse, though differential tumor contamination of PBSC compared to BMSC has not been demonstrated. A recent report from investigators in Nebraska suggested favorable outcomes for good risk NHL patients undergoing autotransplantation with PBSC compared to BMSC [7] while recent findings from the same institution showed no advantage of PBSC for patients with Hodgkin's disease [32]. One recent randomized study of autografts for germ cell tumors compared BMSC to chemotherapy plus cytokine-mobilized PBSC along with post-transplant G-CSF. This report showed modestly quicker trilineage hematologic recovery, but no advantage in other clinical endpoints measured (febrile days, hospital days, survival, or event-free survival) [27].

The small size of our randomized study led us to expand analyses to include the non-randomized data, as well. We are aware that such assignment introduces the possibility of bias by factors known or unknown affecting the assignment. Acknowledging this possibility, we have used statistical models to correct for known covariates. We have therefore reported both the randomized and assigned patients' data and considered randomization vs. assignment as a covariate within the combined regression models. We are more confident in the validity of this approach because of the consonance in effects observed when the randomized and non-randomized subgroups were analyzed separately.

In the current series, multivariate analyses demonstrated no reduction in relapse risk associated with the use of PBSC for either NHL or HD patients, having either responsive or resistant disease at transplantation. This comparative trial has demonstrated no advantage for non-mobilized PBSC over BMSC for use in transplantation, even in patients with prior marrow tumor involvement. Additional formal study will be required to test the clinical advantages of mobilized PBSC as an alternative to autologous bone marrow transplantation for patients with lymphoma.

ACKNOWLEDGMENTS

Supported in part by a grant from the National Cancer Institute (CA21737). B.R.B. is a recipient of the Edward Mallinkrodt Jr. Scholar Award. J.H.K. is a recipient of an Outstanding Investigator Award (CA49721) from the NCI.

REFERENCES

1. Philip T, Armitage JO, Spitzer G, Chauvin F, Jagannath S, Cahn J-Y, Colombat P, Goldstone AH, Gorin NC, Flesh M, Laporte J-P, Maraninchi D, Pico J, Bodly A, Anderson C, Schots R, Biron P, Cabanillas F, Dicke K: High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults in intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med 316:1493, 1987.
2. Philips GL, Fay JW, Herzig RH, Lazarus HM, Wolff SN, Lin H-S, Shina DC, Glasgow GP, Griffith RC, Lamb CW, Herzig GP: The treatment of progressive non-Hodgkin's lymphoma with intensive chemoradiotherapy and autologous marrow transplantation. Blood 75: 831, 1990.
3. Petersen FB, Appelbaum FR, Hill R, Fisher CD, Bigelow CL, Sanders JE, Sullivan KM, Bensinger WI, Witherspoon RP, Storb R, Clift RA, Fefer A, Press OW, Weiden PL, Singer J, Thomas ED, Buckner CD: Autologous marrow transplantation for malignant lymphoma: A report of 101 cases from Seattle. J Clin Oncol 8:638, 1990.
4. Goldstone AH, Singer CRJ, Gribben JG, McMillan A: Experience of autologous bone marrow transplantation in the first 100 lymphomas. Bone Marrow Transpl 3 (Suppl 1):65, 1988.
5. Kessinger A, Vose JM, Bierman PJ, Armitage JO: High-dose therapy and autologous peripheral stem cell transplantation for patients with bone marrow metastases and relapsed lymphoma: An alternative to bone marrow purging. Exp Hematol 19:1013, 1991.
6. Weisdorf DJ, Haake R, Miller WJ, McGlave PB, LeBien TW, Vallera DA, Lasky LC, Kim TH, Peterson BA, Ramsay NKC, Kersey JH, Hurd DD: Autologous bone marrow transplantation for progressive non-Hodgkin's lymphoma: Clinical impact of immunophenotype and in vitro purging. Bone Marrow Transpl 8:135, 1991.
7. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, Gordon B, Armitage JO: High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. J Clin Oncol 11:1846, 1993.
8. Gulati S, Yahalom J, Acaba L, Reich L, Motzer R, Crown J, Toia M, Igarashi T, Lemoli R, Hanninen E, Doherty M: Treatment of patients with relapsed and resistant non-Hodgkin's lymphoma using total body

irradiation, etoposide, and cyclophosphamide and autologous bone marrow transplantation. J Clin Oncol 10:936, 1992.
9. Hurd DD, Haake RJ, Lasky LC, Christiansen NP, McGlave PB, Bostrom B, Levine EG, Weisdorf DJ, Kim TH, Peterson BA, Bloomfield CD: Treatment of refractory and relapsed Hodgkin's disease: Intensive chemotherapy and autologous bone marrow or peripheral blood stem cell support. Med Pediat Oncol 18:447, 1990.
10. Freedman AS, Takvorian T, Anderson KC, Mauch P, Rabinowe SN, Blake K, Yeap B, Soiffer R, Coral F, Heflin L, Ritz J, Nadler LM: Autologuous bone marrow transplantation in B-cell non-Hodgkin's lymphoma: Very low treatment-related mortality in 100 patients in sensitive relapse. J Clin Oncol 8:784, 1990.
11. To LB, Roberts MM, Haylock DN, Dyson PG, Branford AL, Thorp D, Ho JQK, Dart GW, Horvath N, Davy MLJ, Olweny CLM, Abdi E, Juttner CA: Comparison of haematological recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic bone marrow transplants. Bone Marrow Transpl 9:277, 1992.
12. Henon R, Liang H, Beck-Wirth G, Eisenmann JC, Lepers M, Wunder E, Kandel G: Comparison of hematopoietic and immune recovery after autologous bone marrow or blood stem cell transplants. Bone Marrow Transpl 9:385, 1992.
13. Sharp JG, Crouse DA: Marrow contamination: Detection and significance. In Armitage JO, Crouse DA, eds: ''High-Dose Cancer Therapy: Pharmacology, Hematopoietins, Stem Cells.'' Baltimore: Williams & Wilkins, 1992.
14. Weisdorf D, Katsanis E, Verfaillie C, Ramsay NKC, Haake R, Garrison L, Blazar BR: IL-1α administered after autologous transplantation: A Phase I/II clinical trial. Blood 84:2044, 1994.
15. Weisdorf DJ, Verfaillie CM, Davies SM, Filipovich AH, Wagner JE Jr, Miller JS, Burroughs J, Ramsay NKC, Kersey JH, McGlave PB, Blazar BR: Hematopoietic growth factors for graft failure after bone marrow transplantation: A randomized trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) versus sequential GM-CSF plus granulocyte-CSF. Blood 85:3452, 1995.
16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958.
17. Cox DR: Regression models and life tables. J R Stat Soc Series B 34:187, 1972.
18. Lobo F, Kessinger A, Landmark JD, Smith DM, Weisenburger DD, Wigton RS, Armitage JO: Addition of peripheral blood stem cells collected without mobilization techniques to transplanted autologous bone marrow did not hasten marrow recovery following myeloablative therapy. Bone Marrow Transpl 8:389, 1991.
19. To LB, Shepperd KM, Haylock DN, Dyson PG, Charles P, Thorp DL, Dale BM, Dart GW, Roberts MM, Sage RE, Juttner CA: Single high doses of cyclophosphamide enable the collection of high numbers of hematopoietic stem cells from the peripheral blood. Exp Hematol 18: 442, 1990.
20. Siena S, Bregni M, Brando B, Ravagnari F, Bonadonna G, Gianni AM: Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: Enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. Blood 74:1905, 1989.
21. Chao NJ, Schriber JR, Grimes K, Long GD, Negrin RS, Raimondi CM, Horning SJ, Brown SL, Miller L, Blume KG: Granulocyte colony-stimulating factor ''mobilized'' peripheral blood progenitor cells accelerate granulocyte and platelet recovery after high-dose chemotherapy. Blood 81:2031, 1993.
22. Bishop MR, Anderson JR, Jackson JD, Bierman PJ, Reed EC, Vose JM, Armitage JO, Warkentin PI, Kessinger A: High-dose therapy and peripheral blood progenitor cell transplantation: Effects of recombinant human granulocyte-macrophage colony-stimulating factor on the autograft. Blood 83:610, 1994.
23. Peters WP, Rosner G, Ross M, Vredenburgh D, Meisenberg B, Gilbert C, Kurtzberg J: Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. Blood 81:1709, 1993.
24. Pettengell R, Morgenstern GR, Woll PJ, Chang J, Rowlands M, Young R, Radford JA, Scarffe JH, Testa NG, Crowther D: Peripheral blood progenitor cell transplantation in lymphoma and leukemia using a single apheresis. Blood 82:3770, 1993.
25. Nademanee A, Sniecinski I, Schmidt GM, Dagis AC, O'Donnell MR, Snyder DS, Parker PM, Stein AS, Smith EP, Molina A, Stepan DE, Somlo G, Margolin KA, Woo D, Niland JC, Forman SJ: High-dose therapy followed by autologous peripheral-blood stem-cell transplantation for patients with Hodgkin's disease and non-Hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor-mobilized peripheral-blood stem cells. J Clin Oncol 12:2176, 1994.
26. Elias AD, Ayash L, Anderson KC, Hunt M, Wheeler C, Schwartz G, Tepler I, Manzanet R, Lynch C, Pap S, Pelaez J, Reich E, Critchlow J, Demetri G, Bibbo J, Schnipper L, Griffin JD, Frei E III, Antman KH: Mobilization of peripheral blood progenitor cells by chemotherapy and granulocyte-macrophage colony-stimulating factor for hematologic support after high-dose intensification for breast cancer. Blood 79:3036, 1992.
27. Beyer J, Schwella N, Zingsem J, Stroscheer I, Schwaner I, Oettle H, Serke S, Huhn D, Stieger W: Hematopoietic rescue after high-dose chemotherapy using autologous peripheral-blood progenitor cells or bone marrow: A randomized comparison. J Clin Oncol 13:1328, 1995.
28. Hardingham JE, Kotasek D, Sage RE, Dobrovic A, Gooley T, Dale BM: Molecular detection of residual lymphoma cells in peripheral blood stem cell harvests and following autologous transplantation. Bone Marrow Transpl 11:15, 1993.
29. Gribben JG, Freedman AS, Neuberg D, Roy DC, Blake KW, Woo SD, Grossbard ML, Rabinowe SN, Coral F, Freeman GJ, Ritz J, Nadler LM: Immunologic purging of marrow assessed by PCR before autologous bone marrow transplantation for B-cell lymphoma. N Engl J Med 325:1525, 1991.
30. Gribben JG, Freedman AS, Woo SD, Blake K, Shu RS, Freeman G, Longtine JA, Pinkus GS, Nadler LM: All advanced stage non-Hodgkin's lymphomas with a polymerase chain reaction amplifiable breakpoint of bcl-2 have residual cells containing the bcl-2 rearrangement at evaluation and after treatment. Blood 78:3275, 1991.
31. Brenner MK, Rill DR, Moen RC, Krance RA, Mirro J Jr, Anderson WF, Ihle JN: Gene-marking to trace origin of relapse after autologous bone-marrow transplantation. Lancet 341:85, 1993.
32. Bierman P, Vose J, Anderson J, Bishop M, Pierson J, Armitage J, Kessinger A: Comparison of autologous bone marrow transplantation (ABMT) with peripheral stem cell transplantation (PSCT) for patients (PTS) with Hodgkin's Disease (HD). Blood 82(Suppl):445a, 1993.